degradation. See p. 11, first paragraph. For example, in some embodiments it is preferred that compression pressures in excess of 2000 psi/gram are avoided.

Thyroid hormones undergo undesirable degradation when reacted with water. Excipients commonly used to make dosage forms of thyroid hormone comprise residual moisture. Stabilized drug dosage forms can be achieved by preparing the drug dosage form using methods that limit the exposure of thyroid hormones to the residual moisture found in excipients.

When a dosage form is made using high compression techniques a substantial portion of residual moisture in an excipient is forced from the interior bulk of the excipient to the exterior bulk of the excipient that is in contact with the thyroid hormone. Thus, dosage forms made using high compression techniques unnecessarily react the thyroid hormone with water thereby causing undesirable degradation of the thyroid hormone.

In contrast to the Applicants' invention, U.S. Patent No. 5,225,204 to Chen et al. teaches a dosage form of levothyroxine sodium comprising a complex of levothyroxine sodium and water soluble polyvinylpyrrolidone adsorbed on a cellulose compound. The complexes are mixed with pharmaceutically acceptable excipients and then compressed into tablets. The Chen patent teaches that a "tablet machine [is] used to compress the resulting dry mixture into tablets." Example 2. The Chen patent does not teach dosage forms that are compressed at pressures that avoid the exacerbation of moisture induced degradation of thyroid hormone. Indeed, the Chen patent does not recognize that dosage forms prepared under conditions of high pressure will increase the moisture induced degradation of thyroid hormone. Thus, the Chen reference does not teach dosage forms prepared *under conditions of low compression*.

Claim Rejections – 35 U.S.C. §112, 2nd para.

Claims 8, 19, 78, and 79 have been rejected under 35 U.S.C. §112, 2nd paragraph as indefinite. This rejection is respectfully traversed as to claims 8 and 19 as these claims recite subject matter with a reasonable degree of clarity to one of ordinary skill in the art. See M.P.E.P. §§2173.01-2173.02

The Office Action asserts that "it is unclear whether all the ingredients are excipients in the formulation or if each ingredient is a separate member of a group of excipients." See Office Action at p. 3. Claims 8 and 19 contemplate an excipient that includes hydroxypropyl methylcellulose, carboxymethyl cellulose, microcrystalline cellulose, amorphous silicon dioxide, magnesium stearate, starch, sodium starch glycolate, **or** combinations thereof. One of ordinary skill understands that the list of species and phrase "**or** combinations thereof" indicate that any individual species or a combination of the species is the excipient in the formulation. Applicant appreciates the claim language suggested in the Office Action, but such claim amendment is not consistent with the scope of Applicant's invention.

Claims 78 and 79 have been amended to address the concerns of the Examiner. Accordingly, withdrawal of the rejection of claims 8, 19, 78, and 79 under 35 U.S.C. §112, 2nd paragraph are respectfully requested.

Claim Rejections – 35 U.S.C. §102(b)

In the Office action claims 1-2, 4-8, 10-13, 15-19, 21-23, and 78-79 have been rejected under 35 U.S.C. §102(b) as allegedly being unpatentable over the Chen patent. This rejection is respectfully traversed as the Chen patent does not teach every element of the claimed invention.

As will be shown, the Chen patent does not teach every element of claims 1-2, 4-8, 10-13, 15-19, 21-23, and 78-79 because the Chen patent does not teach dosage forms comprising thyroid hormone prepared under conditions that avoid the exacerbation of moisture induced degradation, i.e., *conditions of low compression*. Example 2 of the Chen patent teaches that a tablet machine is used to compress the dry dosage forms into tablets, but does not specify a compaction pressure. See Col. 7, lines 16-17. The Chen specification does not expressly teach a method of compacting the dry dosage form at pressures that avoid the exacerbation of moisture induced degradation of thyroid hormone. Without such a teaching, the present claims cannot be found to be anticipated by the Chen patent.

Accordingly, since the Chen patent does not teach or suggest all of the elements of Applicant's claims 1-2, 4-8, 10-13, 15-19, 21-23, and 78-79, withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Claim Rejections – 35 U.S.C. §103(a)

Claims 1-2, 4-13, 15-23, and 78-79 are rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over the Chen patent. Claims 1-2, 4-13, 15-23, and 78-79 are also rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over the Chen patent in view of U.S.

Patent No. 5,955,105 to Mitra, or in view of U.S. Patent No. 4,001,211 to Sarkar, or in view of U.S. Patent No. 5,756,123 to Yamamoto.

As will be shown, the Chen, Mitra, Sarkar, and Yamamoto patents do not teach or suggest every element of claims 1-2, 4-13, 15-23, and 78-79 because the Chen, Mitra, Sarkar, and Yamamoto patents do not direct the art skilled to dosage forms *prepared under conditions of low compression.*

The Mitra patent teaches thyroid hormone preparations comprising thyroxine drugs, an inorganic salt, a carbohydrate having a molecular weight greater than 500, and glycine. The preparations have a free water content less than 4.5 percent by weight of the preparation. The Mitra patent teaches preparations that are prepared as a direct compression formula, e.g., by using a tablet press. Col. 4, lines 60-61; col. 6, lines 5-6. While the Mitra patent does not expressly preclude preparing formulations *under conditions of low compression*, there is simply no suggestion to utilize the same. And without such a suggestion, the Mitra patent cannot be found to teach dosage forms that are compressed at pressures that avoid the exacerbation of moisture induced degradation of thyroid hormone. Indeed, the Mitra patent does not recognize that dosage forms prepared under conditions of high pressure will increase the moisture induced degradation of thyroid hormone. Thus, the Mitra reference does not teach dosage forms prepared *under conditions of low compression.*

The Sarkar patent teaches thermogelling methyl cellulose ether compositions for use in preparing pharmaceutical capsules. The Sarkar patent does not teach dosage forms that are compressed at pressures that avoid the exacerbation of moisture induced degradation of thyroid

hormone. Thus, the Sarkar patent does not teach dosage forms comprising thyroid hormone and a pharmaceutically acceptable excipient *prepared under conditions of low compression.*

The Yamamoto patent teaches a capsule shell comprising hydroxypropylmethyl cellulose, carrageenan, and potassium ion and/or calcium. The Yamamoto patent does not teach dosage forms that are compressed at pressures that avoid the exacerbation of moisture induced degradation of thyroid hormone. Thus, the Yamamoto patent does not teach dosage forms comprising thyroid hormone and a pharmaceutically acceptable excipient *prepared under conditions of low compression.*

As described above, the Chen, Mitra, Sarkar, and Yamamoto patents do not teach solid dosage forms made *using low compression techniques.* There is simply no suggestion to utilize the same. Without such a suggestion, the present claims cannot be found obvious over the Chen, Mitra, Sarkar, and Yamamoto patents.

The Office Action points to no legally sufficient motivation for its proposed modification of the cited reference. Since there is no suggestion in the prior art of record of dosage forms *prepared under conditions of low compression*, there cannot be motivation to modify the cited art to achieve the methods of the present invention. Accordingly, since the Chen, Mitra, Sarkar, and Yamamoto patents do not teach or suggest all of the elements of Applicant's claims 1-2, 4-13, 15-23, and 78-79, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Claims 1, 5-12, 16-23, and 78-79 are rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over the Mitra patent in view of U.S. Patent No. 4,389,393 to Schor, or in view of U.S. Patent No. 4,983,399 to Maish.

The Schor patent teaches a carrier base material combined with a therapeutically active medicament, such as for example, a thyroid preparation, shaped and compressed to a solid unit dosage form having a regular and prolonged release pattern upon administration. Although the Schor patent teaches that tablets may be formed in a conventional tableting machine at compression pressures of 2,000 to 16,000 lbs/in^2, the Schor patent does not teach dosage forms prepared under compression conditions that avoid the exacerbation of moisture induced degradation of thyroid hormone.

Moreover, the teaching of compression pressures in the Schor patent, e.g., 2,000 to 16,000 lbs/in^2, is *meaningless without knowing the mass of the tablet being compressed.* For example claims 5, 6, 7, 16, 17, 18 recite a compaction pressure in units of pressure per mass. The Schor patent teaches the preparation of tablets having a mass of less than one gram. For example, Example 6 describes the preparation of a 717 mg tablet by compressing it at 5000 psi. A compression pressure of 5000 psi applied to a 717 mg tablet yields a compression pressure of 6973.5 psi/gram. Thus, the Schor patent does not teach dosage forms comprising thyroid hormone and a pharmaceutically acceptable excipient *prepared under conditions of low compression.*

The Maish patent teaches a direct compression carrier composition comprising one or more cellulose carboxylic acid esters and a lubricant useful in the preparation of tablets containing acetaminophen. The acetaminophen compositions may be compressed into tablets using conventional tableting equipment and compression forces between 2000 and 3000 lbs/in^2. See Col. 2, lines 30-33. Examples 7 and 8 show that acetaminophen tablets having a mass of less

than 1 gram can be compressed at 1000, 2000, 3000, and 4000 lbs/in^2. The Maish patent does not teach dosage forms of thyroid hormone.

Moreover, the Maish patent does not teach dosage forms prepared under compression pressures that avoid the exacerbation of moisture induced degradation of thyroid hormone. Thus, the Maish patent does not teach dosage forms comprising thyroid hormone and a pharmaceutically acceptable excipient *prepared under conditions of low compression.*

As described above, the Mitra, Schor, and Maish patents do not teach dosage forms comprising thyroid hormone and a pharmaceutically acceptable excipient prepared under compression pressures that avoid the exacerbation of moisture induced degradation of thyroid hormone. Thus, the Mitra, Schor, and Maish patents do not teach solid dosage forms *prepared under conditions of low compression.* There is simply no suggestion to utilize the same. Without such a suggestion, the present claims cannot be found obvious over the Mitra, Schor, and Maish patents.

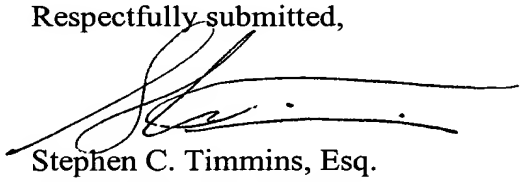
The Office Action points to no legally sufficient motivation for its proposed modification of the Mitra, Schor, and Maish patents. Since there is no suggestion in the prior art of record of dosage forms prepared under compression pressures that avoid the exacerbation of moisture induced degradation of thyroid hormone there cannot be motivation to modify the cited art to achieve the present invention. Accordingly, since the Mitra, Schor, and Maish patents do not teach or suggest all of the elements of Applicant's claims 1, 5-12, 16-23, and 78-79, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

Applicant believes that the foregoing is a full and complete response to the Office Action of record. Accordingly, an early and favorable reconsideration of the rejections and allowance of all of pending claims 1-23, 78-79, and 90-92 are respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE"**.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

New claims 90, 91, and 92 have been added.

Please amend claims 78 and 79 as follows:

78. (**Amended**) A method of administering a thyroid hormone to a patient comprising providing a unit dose of the thyroid hormone which has not been processed employing high compression.

79. (**Amended**) A method for administering levothyroxine to a patient comprising providing a unit dose of [the] levothyroxine which has not been processed employing high compression.